Journal of Surgical Oncology 63:125–129 (1996)

Tumor-induced Hypercalcemia in a Patient With Extensive Soft Tissue Sarcoma: Effects of Bisphosphonate Therapy and Surgery

VÉRONIQUE OLEFFE, MD, JEAN-CLAUDE DUMON, AND JEAN-JACQUES BODY, MD, PhD
From the Bone Metabolism Unit, Service de Médecine et Laboratoire d'Investigation Clinique H.J. Tagnon, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Tumor-induced hypercalcemia (TIH) is a frequent complication of advanced cancer, but it has been rarely reported in patients with sarcoma. We describe the case of a young female patient with TIH and with an extensive synoviosarcoma of the left lower limb destroying the bony structures. Hypercalcemia was severe (18.3 mg/dl) and accompanied by low serum P_i and suppressed parathyroid hormone (PTH) and $1,25(OH)_2$ vit D_3 serum concentrations. Hypercalcemia was successfully treated with ibandronate, a new third-generation bisphosphonate, and radical surgery was performed when the patient was normocalcemic. Circulating levels of PTH-related protein (PTHrP) were elevated at 22.5 pmol/L (NI <9). PTHrP levels did not change after successful therapy of TIH, in contrast with PTH, which increased sharply. PTHrP levels were normalized after radical surgery. Moreover, low serum Pi with reduced threshold for phosphate excretion and increased tubular calcium reabsorption supported the notion that PTHrP was indeed the essential mediator of paraneoplastic hypercalcemia in this case despite the extensive bone destruction.

KEY WORDS: **bone, osteolysis, cancer, parathyroid**

INTRODUCTION

Tumor-induced hypercalcemia (TIH) is one of the most frequent paraneoplastic syndromes, occurring in 10–15% of patients with advanced cancer [1]. TIH is classically divided into hypercalcemia complicating metastatic bone disease, humoral hypercalcemia of malignancy (HHM), and hypercalcemia of hematological neoplasms [1,2]. However, the boundaries among these three types of TIH progressively fade as the essential pathogenic role of parathyroid hormone-related protein (PTHrP) becomes more evident in all types of TIH [3,4]. Circulating levels of PTHrP are thus elevated in virtually all patients with HHM and, depending on the assay, in up to two-thirds of patients with breast cancer and TIH [4,5].

Ectopic secretion of PTHrP constitutes a primary phenomenon of pathogenic importance in patients with TIH, and we and others have shown that PTHrP levels do not change after successful therapy of TIH with bisphosphonates [6–8]. However, the data are quite scarce concerning the effects of successful antineoplastic treatment on PTHrP levels, as TIH most often complicates advanced and refractory cancer [1,9].

We report the case of a patient with TIH, within the framework of a locally advanced synoviosarcoma of the lower limb. The patient was first treated by a third-generation bisphosphonate, then by radical surgery when normocalcemia was attained. Biochemical parameters of bone metabolism were closely followed and clearly illustrate the pathogenesis of TIH of humoral origin.

Accepted for publication May 18, 1996.

Address reprint requests to J.J. Body, M.D., Ph.D., Bone Metabolism Unit, Service de Médecine et Laboratoire d'Investigation Clinique H.J. Tagnon, Institut Jules Bordet, Université Libre de Bruxelles, Rue Héger-Bordet 1, 1000 Brussels, Belgium.

METHODS

Case History

A 23-year-old Lebanese woman was referred to our institution for surgical treatment of a malignant tumor of the left lower limb. The tumor first appeared 7 years before the admission as a swelling localized above the left ankle. She was initially treated by limited surgery, but a more extensive surgical procedure had to be performed 3 years later. The procedure then involved curettage of the left tibia and reconstruction by bone graft and internal orthopedic fixation with a plaque and nails. A third exploratory intervention was performed 3 years later for massive local recurrence. Cancer was diagnosed, and the patient was referred to us for further treatment.

Examination demonstrated massive tumor involvement of the left lower limb from the ankle almost up to the knee. The skin was ulcerated above the ankle. Pain was severe, and the patient had to be placed on narcotics. She also complained of polyuria and polydypsia of several weeks' duration; she was somnolent and clinically dehydrated. Radiographs of the lower left limb revealed a tumor process, apparently starting from the soft tissues and almost completely destroying the lower half of the tibia and fibula (Fig. 1). Laboratory tests indicated severe hypercalcemia at 18.3 mg/dl (NI <10.5 mg/dl); she was treated initially with 3 L of saline per 24 hr, over 36 hr. After rehydration, she was treated by a third-generation bisphosphonate, ibandronate (BM 21.0955, Boehringer-Mannheim, Germany) at a dose of 2 mg in 500 ml saline IV over 2 hr [10,11].

Radical surgery was performed after the patient had become normocalcemic and we could monitor separately the effects of bisphosphonate therapy and of surgery on biochemical parameters of calcium and bone metabolism.

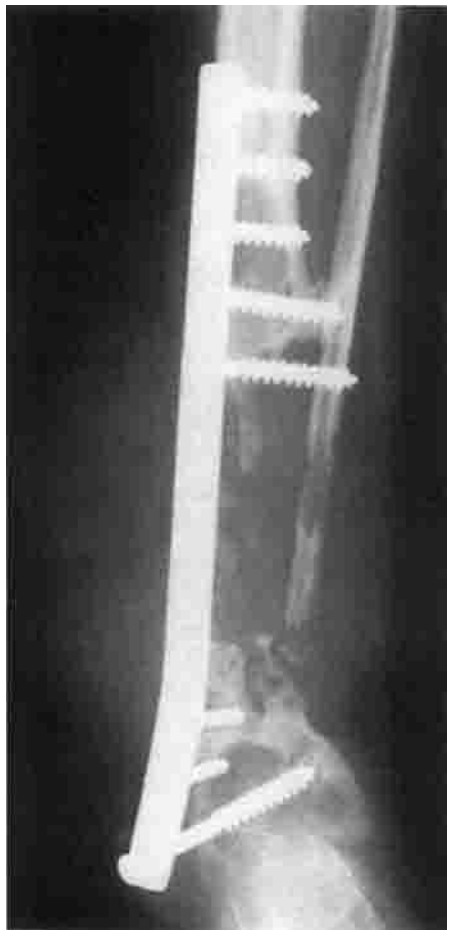

Fig. 1. Radiograph of the lower left limb showing a massive tumor largely destroying bony structures. Prosthetic material dates from an operation performed 3 years earlier.

Laboratory Determinations

As previously described [12–16], serum parameters included total serum Ca (normal values, NI 8.5–10.3 mg/dl), ionized Ca (Ca^{2+}, measured by the Ciba-Corning electrode; NI 4.2–5.1 mg/dl), calcium levels corrected for protein concentrations according to Parfitt's formula [12] (corrected Ca; NI 8.5–10.5 mg/dl), inorganic phosphate (P_i; NI 2.2–4.5 mg/dl), intact parathyroid hormone (PTH; NI, 10–50 pg/ml) [14], alkaline phosphatase (Alk Phos; NI <110 mU/ml), osteocalcin (NI 1–6 ng/L) [15], vitamin D (NI, 15–50 ng/ml) $1,25(OH)_2$ vit D_3 (NI 15–42 pg/ml), and PTH-related protein (PTHrP), measured with a commercially available N-terminal radioimmunoassay (NI <9 pmol/L [7]). All assays were bought from INCSTAR (Stillwater, MN).

Urine measurements in 2-hr fasting morning samples [13,16] included calcium, phosphate, and creatinine to derive indexes of bone resorption, namely Ca/creatinine (NI <0.21 mg/mg) and hydroxyproline (NI <4.7 mg × 100/mg creatinine). We also calculated the renal threshold phosphate index, i.e., TmP/glomerular filtration rate (GFR) (NI 2.5–4.2 mg/dl) [17] and an index of the renal reabsorption of calcium, using an algorithm provided by J.P. Bonjour, Geneva (TRCal; NI 2.36–2.86 mmol/L [18].

BIOCHEMICAL AND CLINICAL EVOLUTION

Ca (corrected for protein levels) was 18.3 mg/dl before therapy; hypercalcemia was confirmed by measurement of Ca^{2+} (9.52 mg/dl). Serum phosphorus (P_i) level was 2.8 mg/dl, and parameters of liver and renal function were normal. Rehydration lowered Ca levels down to 16.4 mg/dl with a drop in P_i levels to 1.9 mg/dl before initiation of bisphosphonate therapy (Figs. 2, 3, respectively). Serum Ca concentrations were normalized 4 days after ibandronate administration (Fig. 2), whereas a further drop in P_i levels down to 1.1 mg/dl was noted (Fig. 3, upper panel). Additional biochemical investigations confirmed that hypercalcemia was not of parathyroid origin (pretreatment PTH levels were low at 10 pg/ml) or due to

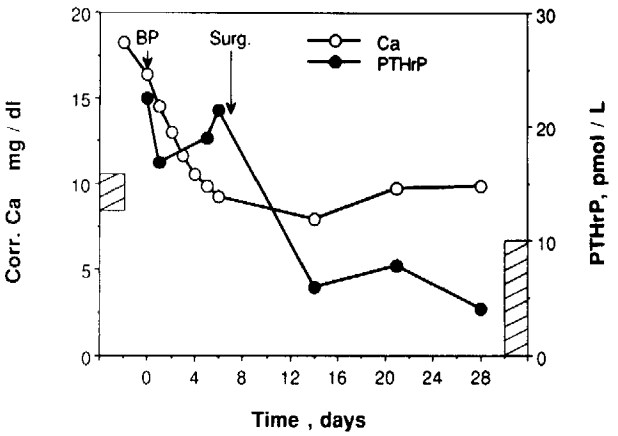

Fig. 2. Serum Ca, corrected for protein levels, and plasma PTHrP concentrations during the clinical course. BP indicates the timing of bisphosphonate administration and Surg the surgery performed with curative intent. Boxes along the y axes indicate the normal range for each parameter. PTHrP, parathyroid hormone-related protein.

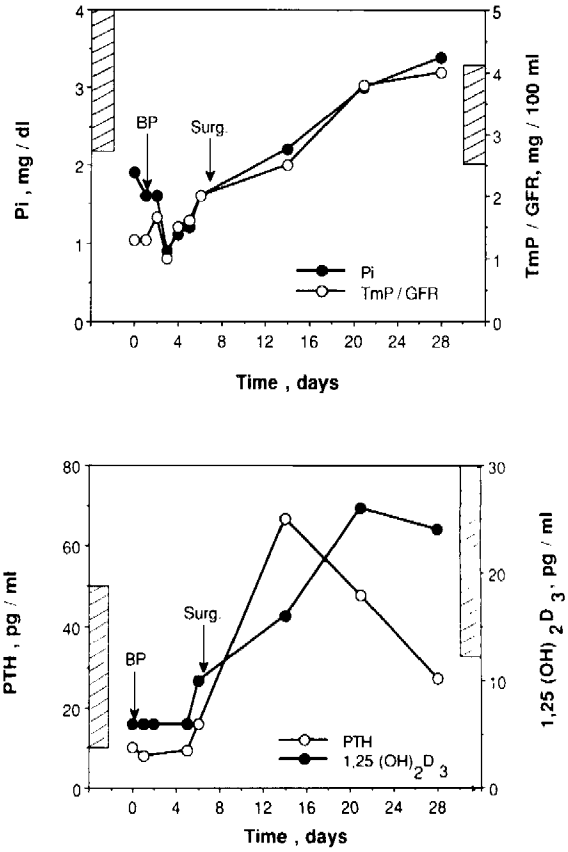

Fig. 3. Upper panel: Concentrations of serum phosphorus (P_i) and the index of renal tubular reabsorption of phosphate (TmP/GFR). Lower panel: Serum intact parathyroid hormone (PTH) and 1,25$(OH)_2$ vit D_3 levels during the clinical course. Abbreviations as in Figure 2.

vitamin D intoxication (several determinations were between 2.5–8.5 ng/ml). The pretreatment levels of 1,25$(OH)_2$ vit D_3, the active metabolite of vitamin D_3, were also low at <6 pg/ml. Circulating PTHrP concentrations, however, were markedly elevated at 22.5 pmol/L. Other parameters of calcium metabolism were as follows: Ca/creatinine was elevated at 0.87 mg/mg, as well as hydroxyproline excretion, which was increased at 13.3 (mg hydroxyproline × 100/mg creatinine). Alkaline phosphatase concentration was normal (100 mU/ml), but osteocalcin concentration was slightly increased at 7.4 ng/ml. These values indicate a marked increase in bone turnover, particularly of bone resorption [13,15,16].

The decline in Ca levels (Fig. 2) was accompanied by an improvement in clinical status. When normocalcemic, the patient could be operated by distal transfemoral amputation and node removal in the inguinocrural region, as preoperative echography had shown the presence of pathological nodes in that region. Tumor histology was consistent with a synoviosarcoma metastatic to regional lymph nodes. The patient was treated with curative intent and returned to her country after an external prosthesis had been placed.

Following surgery, a further decrease in serum Ca was noted, but especially a normalization of plasma PTHrP levels (Fig. 2). As shown in Figure 3, P_i levels declined after bisphosphonate administration but returned to normal values after tumor removal and normalization of PTHrP levels. The threshold for tubular P_i reabsorption (TmP/GFR) was low before surgery, did not change after bisphosphonate therapy, and, as for P_i levels, increased after surgery. Serum concentrations of PTH and 1,25$(OH)_2$ vit D_3 were suppressed when the patient was hypercalcemic and sharply increased when normocalcemia was reached (Fig. 3). Before treatment, the TRCal index was increased at 3.74 mmol/L. There was a steady decrease in fasting urinary Ca excretion after bisphosphonate therapy; the relationship between serum Ca and urinary Ca excretion in our patient is depicted in Figure 4. Urinary calcium excretion was always lower than what it should have been (hatched area) while she was hypercalcemic [19], indicating increased tubular reabsorption of calcium, contributing to significant kidney involvement in the genesis of hypercalcemia [18,20].

DISCUSSION

TIH appears to be a rare complication of sarcoma [21,22], although Burt and Brennan [23] report an incidence of 7% in a large series of patients with various cancers. To the best of our knowledge, detailed clinical and biochemical evaluation of a case of paraneoplastic hypercalcemia complicating a sarcomatous tumor has never been reported [24]. Bisphosphonates have considerably simplified and improved the management of TIH, and pamidronate or newer compounds can successfully correct TIH in 80–90% of cases [3,11,13,21]. Our patient was treated with ibandronate, a new potent third-genera-

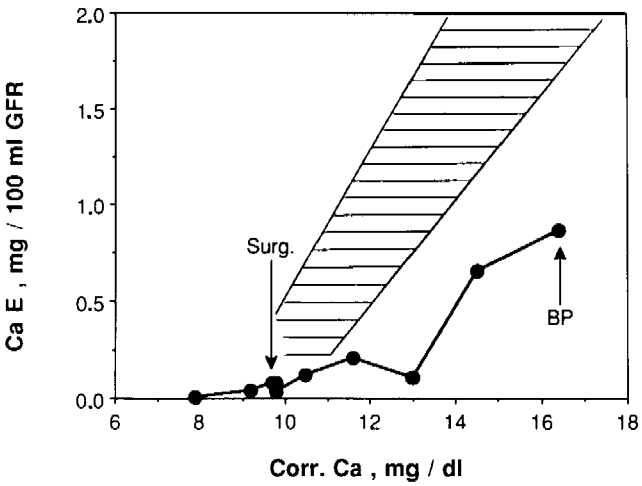

Fig. 4. Relationship between urinary excretion of Ca related to glomerular filtration rate (CaE, mg/dl GFR or UCa/U/P creatinine) and serum Ca levels following bisphosphonate (BP) and surgical (Surg) therapy. Both are related to the normal relationship between those two parameters, as derived from the work of Peacock et al. [19].

tion bisphosphonate, and normocalcemia was quickly attained [11].

The pathogenesis of TIH appears to be particularly interesting in this case. Radiography demonstrated a massive bone destruction due to local invasion of the tumor (Fig. 1), confirmed by pathological examination of the tumor, as the lower part of the tibia and fibula could not even be found in the tumor mass. It is most likely, however, that TIH in this case was essentially mediated by an ectopic secretion of PTHrP, which appears to be the major pathogenic factor in TIH [1–8]. Plasma PTHrP concentrations were markedly elevated in our patient, considering the assay used [7]. Moreover, the low serum P_i levels and the reduced TmP/GFR strongly advocate against a major role of direct osteolysis and favor the essential role of PTHrP in the genesis of TIH in our patient, as PTHrP exhibits marked phosphaturic action [1–3]. Finally, as shown in Figure 4, urinary calcium excretion was always abnormally low when related to serum Ca levels, again consistent with the effects of PTHrP on calcium reabsorption at the level of the renal tubules [18,20].

A marked increase in circulating PTH levels was observed when serum Ca became normal, consistent with our previously published findings [14]. The concentrations of $1,25(OH)_2$ vit D_3 increased following the recovery of PTH secretion, but the synthesis of $1,25(OH)_2$ vit D_3 was probably also stimulated by a further decline in serum P_i levels [25]. The exquisite sensitivity of PTH secretion to changes in serum Ca was in marked contrast with the absence of changes in PTHrP levels when serum Ca was normalized by bisphosphonate therapy. Our case report clearly indicates that PTHrP levels were normalized only after tumor removal. Interestingly, as can also be seen in Figure 2, this led to a further slight decrease in Ca levels, probably reflecting the persistent effect of PTHrP at the kidney level, as bisphosphonates act only on bone resorption.

In summary, we report the case of a patient with an extensive soft tissue sarcoma of the lower limb and paraneoplastic hypercalcemia. There was an extensive local bone destruction by the tumor mass, but our findings indicate that TIH was essentially mediated by a paraneoplastic secretion of PTHrP.

ACKNOWLEDGMENTS

The study was partly supported by grants from the Fondation Lefèbvre, Fonds National de la Recherche Scientifique (Belgium, contrast FRSM 3.4577.96 and Télévie Contract 7.4513.93), Fondation Lambeau-Marteau, and les Amis de l'Institut Bordet. The authors thank Mrs. M.A. Lumen for her help in collecting the patient samples.

REFERENCES

1. Body JJ: Metastatic bone disease: Clinical and therapeutic aspects. Bone 13:S57–S62, 1992.
2. Mundy GR: Pathophysiology of cancer-associated hypercalcemia. Semin Oncol 17(suppl5):10–15, 1990.
3. Body JJ: Bone metastases and tumor-induced hypercalcemia. Curr Opin Oncol 4:624–631, 1992.
4. Grill V, Ho P, Body JJ, et al.: Parathyroid hormone-related protein: Elevated levels in both humoral hypercalcemia of malignancy and hypercalcemia complicating metastatic breast cancer. J Clin Endocrinol Metab 73:1309–1315, 1991.
5. Burtis WJ: Parathyroid hormone-related protein: Structure, function and measurement. Clin Chem 38:2171–2183, 1992.
6. Grill V, Murray RML, Ho PWM, et al.: Circulating PTH and PTHrP levels before and after treatment of tumor induced hypercalcemia with pamidronate disodium (APD). J Clin Endocrinol Metab 74:1468–1470, 1992.
7. Body JJ, Dumon JC, Thirion M, Cleeren A: Circulating PTHrP concentrations in tumor-induced hypercalcemia: Influence on the response to bisphosphonate and changes after therapy. J Bone Miner Res 8:701–706, 1993.
8. Burtis WJ, Dann P, Gaich GA, Soifer NE: A high abundance midregion species of parathyroid hormone-related protein: Immunological and chromatographic characterization in plasma. J Clin Endocrinol Metab 78:317–322, 1994.
9. Ralston SH, Gallacher SJ, Patel U, et al.: Cancer-associated hypercalcemia: Morbidity and mortality. Clinical experience in 126 treated patients. Ann Intern Med 112:499–504, 1990.
10. Wüster C, Schöter KH, Thiébaud D, et al.: Methylpentylaminopropylidene-bisphosphonate (BM 21.0955): A new potent and safe bisphosphonate for the treatment of cancer-associated hypercalcemia. Bone Miner 22:77–85, 1993.
11. Pecherstorfer M, Herrmann Z, Body JJ, et al.: A randomized phase II trial comparing different doses of the bisphosphonate ibandronate (BM 21.0955) in the treatment of hypercalcemia of malignancy. J Clin Oncol 14:268–276, 1996.
12. Parfitt AM: Investigation of disorders of the parathyroid glands. J Clin Endocrinol Metab 3:451–474, 1974.
13. Body JJ, Magritte A, Seraj F, et al.: Aminohydroxypropylidene bisphosphonate treatment for tumor-associated hypercalcemia: A randomized comparison between a 3-day treatment and single 24-hour infusions. J Bone Miner Res 4:923–928, 1989.
14. Body JJ, Dumon JC, Seraj F, Cleeren A: Recovery of parathyroid hormone secretion during correction of tumor-associated hypercalcemia. J Clin Endocrinol Metab 74:1385–1388, 1992.
15. Body JJ, Cleeren A, Pot M, Borkowski A: Serum osteocalcin (BGP) in tumor-associated hypercalcemia. J Bone Miner Res 1:523–527, 1986.

16. Body JJ, Delmas PD: Urinary pyridinium cross-links as markers of bone resorption in tumor-associated hypercalcemia. J Clin Endocrinol Metab 74:471–475, 1992.
17. Walton RJ, Bijvoet OLM: Nomogram for derivation of renal threshold phosphate concentration. Lancet 1:309–310, 1975.
18. Bonjour JP, Philippe J, Guelpa G, et al.: Bone and renal components in hypercalcemia of malignancy and responses to a single infusion of clodronate. Bone 9:123–130, 1988.
19. Peacock M, Robertson WG, Nordin BEC: Relation between serum and urinary calcium with particular reference to parathyroid activity. Lancet 1:384–386, 1969.
20. Ralston SH, Alzaid AA, Gallacher SJ, et al.: Clinical experience with aminohydroxypropylidene bisphosphonate (ADP) in the management of cancer-associated hypercalcemia. Q J Med 69;825–834, 1988.
21. Body JJ, Dumon JC: Treatment of tumor-induced hypercalcaemia with the bisphosphonate pamidronate: Dose-response relationship and influence of the tumour type. Ann Oncol 5:359–363, 1994.
22. Muggia FM: Overview of cancer-related hypercalcemia: epidemiology and etiology. Semin Oncol 17(suppl5):3–9, 1990.
23. Burt ME, Brennan MF: Incidence of hypercalcemia and malignant neoplasm. Arch Surg 115:704–707, 1980.
24. Choi YS, Lundy RO: Rhabdomyosarcoma and hypercalcemia. Arch Intern Med 149:1189, 1989.
25. Portale AA, Halloran BP, Morris RC Jr: Physiologic regulation of the serum concentration of 1,25-dihydroxyvitamin D by phosphorus in normal men. J Clin Invest 83:1494–1499, 1989.